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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,176	07/29/2003	Larry S. Barak	033072-116	7178

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EXAMINER	
CHANDRA, GYAN	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/629,176	BARAK ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's cancellation of 8-21 on 29 July 2003 is acknowledged.

Claims 1-7 are examined on the merits.

Priority

This applicants' claim for priority to the application No. 10/095,620 filed on March 12, 2002 and further benefit of U.S. Provisional Application No. 60/275,339, filed March 13, 2001 is put in record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "evenly distributed in the " recited in the claims is indefinite, since neither the specification nor the art provides an unambiguous definition for the term. Is "evenly distributed" limited to cytoplasm or does it encompasses diverse distribution of a detectable molecule in a medium?

Claim 4-5 recite the limitation "control cell" in claim 2. It is not clear what the features of the control cell are.

Double Patenting

Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-47, 55-82 of U.S. Patent No. 5,891,646. Although the conflicting claims are not identical, they are not patentably distinct from each other because the plurality of conjugated protein formed by conjugating an arrestin protein and a detectable molecule that emits detectable energy (fluorescence, radio-isotope, chemiluminescence) in the instant claims is a genus that encompasses β-arrestin protein and the optically detectable molecule in the claims of patent No. 5,891,646. The preferred embodiments of the instant application shown in the example(s) included in the instant application (page 17, line 10), describe β-arrestin protein conjugated with GFP (an optically detectable molecule). This is the same as the preferred embodiment of the patented claims as illustrated in claim 12, for example, of U.S. Patent No. 5,891,646. The test compound of Claim 6 in the instant application is recited in Claims 27, 35, and 43 in the U.S. Patent No. 5,891,646. Applicants' show by obtaining a before and after treatment image of at least one cell containing a GPCR and β-arrestin protein conjugated with GFP, and show that upon the treatment with a compound, and that if the compound is an agonist, β-arrestin protein conjugated with GFP move from towards endocytosomes. The preferred embodiments of the instant application is illustrated in Example 8 on column 21, line 50-60 of U.S. Patent No. 5,891,646 where twelve different members of the β2AR/rhodopsin subfamily of GPCRs were tested. However, translocation of GPCR bound β-arrestin protein would depend on

affinity of the binding between a GPCR and a β-arrestin protein. Stronger the binding greater they will stay together during this movement towards endosomes as recited by Oakley et.al. (J. Biol. Chem. 275:17201-17210, 2000).

Claims 1-7 are also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,4,6-18, 24-26, of U.S. Patent No. 6,110,693. Although the conflicting claims are not identical, they are not patentably distinct from each other because the plurality of conjugated protein formed by conjugating an arrestin protein and a detectable molecule that emits detectable energy (fluorescence, radio-isotope, chemiluminescence) in the instant claims is a genus that encompasses the β-arrestin protein and GFP conjugate in the claims of patent No. 6,110,693. The preferred embodiments of the instant application shown in the example(s) included in the instant application (page 17, line 10), wherein β-arrestin protein conjugated with a detectable molecule the GFP was used. This is the same as the preferred embodiment of the patented claims as illustrated in Example 5 on column 20, line 33 and Example 8 on column 21, line 42 of U.S. Patent No. 6, 110693. The preferred embodiments of Claims 1-5, 7 of the instant application the same as recited on column 14, line 36 to column 15, line 17 of U.S. Patent No. 6, 110693.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Barak et.al. (1999) U.S. Patent No. 5,891,646. Barak et. al. (1999) disclose agonist mediated translocation of β- arrestin-GFP chimera from cell cytoplasm to membrane. The real-time agonist mediated distribution was viewed by a confocal microscope (column 19, line 30 to column 20, line 44). Barak et. al., have described a method of obtaining an image of at least one control test cell before and after treatment with a test compound in their US Patent 5,891,646 on column 14, line 39 to column 15, line 17. Upon performing a meticulous comparison between methods of obtaining an image of the at least one

cell that expresses a GPCR and a β-arrestin-GFP chimera before and after treatment with a test compound as recited in the claims and an automated screening methods on column 14 of U.S. Patents 5,891646, the examiner came to a conclusion that both methods are identical.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 1-7 are also rejected under 35 U.S.C. 102(e) as being anticipated by Barak et.al. (2000) U.S. Patent No. 6,110693. Barak et. al. (2000) disclose agonist mediated translocation of β- arrestin-GFP chimera from cell to membrane. The real-time agonist mediated distribution was viewed by a confocal microscope (column 19, line 35 to column 20, line 43). Barak et. al., have described a method of obtaining an image of at least one control test cell before and after treatment with a test compound in their US Patent 6,110,693 on column 14, line 40 to column 15, line17. Upon performing a meticulous comparison between methods of obtaining an image of the at least one cell that expresses a GPCR and a β-arrestin-GFP chimera before and after treatment with a test compound as recited in the claims and an automated screening methods on

column 14 of U.S. Patents 5,891646, the examiner came to a conclusion that both methods are identical.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vrecl et.al. (Molecular Endocrinology 12: 1818-1829, 1998) in view of Zhang et.al. (J.Biol. Chem. 274:10999-11006, 1999) and Oakley et.al. (J.Biol. Chem. 275:17201-17210).

Vrecl et.al. teach cellular distribution of β-arrestin-GFP in untreated HEK 293 cells expressing GnRH (a GPCR) using a confocal microscope. They show that β-arrestin-GFP was primarily distributed in cytoplasm and upon an agonist treatment, a time-dependent movement of β-arrestin-GFP to cell membrane was observed. Although, Vrecl et.al. suggested that the reason they did not see β-arrestin-GFP

movement in endocytosomes as β-arrestin binds to a phosphorylated GPCR, but they did not teach how a β-arrestin-GFP molecule moves to endosomes.

Zhang et.al. teach that β- arrestin-GFP binds to GPCR in the cytoplasm and upon treatment with a GPCR agonist the β- arrestin-GFP and GPCR complex dissociated before a GPCR translocated in an endocytic vesicle by directly labeling a GPCR receptor in this study.

Oakley et.al. teach that the movement of a detectable molecule either to membrane or to vesicle depends on the affinity of β- arrestin-GFP chimera to a GPCR. If the affinity of a detectable molecule to the GPCR is high and it does not dissociate, then the complex moves to an endocytic vesicle, and if the affinity of the β- arrestin-GFP chimera to a GPCR is low then the complex dissociates, and only a GPCR moves to an enodcytic vesicle and the β-arrestin-GFP moves to the membrane.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to observe the movement of β- arrestin-GFP to endocytic vesicles in cell expressing a GPCR of Vrecl et.al. or Zhang et.al., by expressing a different GPCR as taught by Oakley et.al. that an interaction between a GPCR and an arrestin depends on C-terminal end of the GPCR and its phosphorylation state.

The person of ordinary skill in the art would have been motivated to make those modifications because two different class of GPCRs have variable c-terminal structure and they interact differently with β-arrestin-GFP. The experiment by expressing two different classes of GPCRs separately along with β-arrestin-GFP, would have depicted β-arrestin-GFP movement in an endocytic vesicle.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for β-arrestin-GFP as a detectable molecule, does not reasonably provide enablement for a detectable molecule. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to a method of detecting G protein-coupled receptor pathway activity, comprising at least one cell expressing a GPCR and a plurality of conjugated proteins formed by conjugating an arrestin protein and a detectable molecule. The specification discloses the term "optically detectable molecule" means means any molecule capable of detection by spectroscopic, photochemical, biochemical, immunochemical, electrical, radioactive, and optical means, including but not limited to, fluorescence, phosphorescence, and bioluminescence and radioactive decay. Detectable molecules include, but are not limited to, GFP, luciferase, βgalactosidase, rhodamine-conjugated antibody, and the like. Detectable molecules includeradioisotopes, epitope tags, affinity labels, enzymes, fluorescent groups, chemiluminescent groups, and the like. Detectable molecules include molecules which are directly or indirectly detected as a function of their interaction with other

molecules. General guidance is given regarding how to make and test β-arrestin-GFP in a method of detecting GPCR pathway activity. The scope of patent protection sought by Applicants as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons. The problem of making a chimera with a arrestin protein and other detectable molecules such as luciferase, β-galactosidase, rhoadamine-conjugated antibody or another enzyme is extremely complex. While it is known that many of these molecules have been attached with proteins in different assays but attaching these molecules to an arrestin molecule with a reasonable expectation of success are limited. Oakley et.al. (2000) describe that all three different arrestins (arrestin, β-arrestin1 and β-arrestin2) bind GPCR with different affinity.

A large number of experimentation would be required to make luminescent arrestin or any other detectable molecule fusions that would be detectable because specification dose not provide any details on which luminescent protein to use and how to attach a luminescent protein with β-arrestin protein.

The amount of guidance or direction provided by specification with regard to prepare a detectable molecule with luciferase, β-galactosidase, rhoadamine-conjugated antibody or another enzyme with arrestin is very small and would require a large amount of experimentation.

There are no working examples directed to detectable molecule so that one can easily translate β-arrestin GFP chimera into luciferase, β-galactosidase, rhoadamine-conjugated antibody or another enzyme without undue experimentations.

The state of the art with regard to BRET is evolving. A number of reports have recently been published for the use of this technology in studying cell based high throughput screening assay for monitoring GPCR activation using β-galactosidase (J.Biomolecular Screening 7:451-459,2002).

The detectable molecule system is complex because it requires a person skilled in the field to identify which molecule (e.g., rhoadamine-conjugated antibody or other enzyme) one needs to attach with either β-arrestin1 or β-arrestin2 for detecting GPCR pathway.

It is unpredictable which detectable molecule would work when attached with an arrestin protein to detect the GPCR activation pathway because detectable molecule would require an optimization to where it should be attach without interrupting interaction between an arrestin and the GPCR.

The claims are very broad, in that the claims do not specify which detectable molecules (luciferase, βgalactosidase, rhodamine-conjugated antibody, and the like) and where the detectable molecules should be attached to what positions of arrestins for detecting of GPCR.

Due to the large quantity of experimentation necessary to determine a detectable molecule and arrestin fusion such that it can be determined how to use the claimed detectable molecule, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that the detectable molecule can not be predicted based on β-arrestin-GFP information, and the breadth of

the claims which fail to recite particular luminescent, or other enzymes, the specification fails to teach the skilled artisan how to make and use the claimed invention.

The claims are directed to a method of detecting G protein-coupled receptor pathway activity, comprising at least one cell expressing a GPCR and a plurality of conjugated proteins formed by conjugating an arrestin protein and a detectable molecule. The specification discloses the term "arrestin" refers to all types of naturally occurring and engineered variants of arrestin, including, but not limited to, visual arrestin (referred to as Arrestin 1), βarrestin 1 (referred to as Arrestin2), and βarrestin 2 (referred to as Arrestin 3). The specification further establishes movement of β-arrestin2-GFP from cytosol to endosome when the HEK-293 cells containing vasopressin V2 receptor (V2R) were treated with an agonist. General guidance is provided regarding detecting an image of cells containing a GPCR and β-arrestin2-GFP chimera before and after treatment with a GPCR agonist to detect β-arrestin2-GFP movement. The scope of patent protection sought by Applicants as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons. The problem of predicting arrestin interaction with a GPCR is extremely complex. While it is known that there are three different arrestin proteins (arrestin1, arrestin2, arrestin3) and over 1000 GPCRs that mediate distinct physiological functions (Oakley et.al., 2000), predicting which arrestin protein will interact with a given GPCR, and whether the complex will move to an endocytic vesicle or to the membrane with a reasonable expectation of success is limited.

A large number of experimentation would be required to show which arrestin would bind with a GPCR and upon an agonist treatment whether the complex would move to an endocytic vesicle. As Oakley et.al. describe that GPCRs contain common arrestin recognition motifs and affinity for different arrestins varies each GPCR. Also, the affinity of an arrestin to a GPCR differs on a number of phosphorylation sites and the state of phosphyrylation of a GPCR.

The amount of guidance or direction provided by specification with regard to prepare a detectable molecule chimera with arrestins is very small and would require a large amount of experimentation. One has take into account that a detectable molecule and an arrestin chimera should not hamper interaction between a GPCR and the arrestins.

There are no working examples directed to predict a GPCR and an arrestin interaction the nature of complex formation and dissociation in *in vivo* without undue experimentations.

The arrestins and a GPCR interaction is complex because it requires a person skilled in the field to identify a GPCR and arrestin binding site, the GPCR phophorylation site(s) to make an arrestin detectable molecule to apply in detecting a GPCR activation pathway.

The claims are very broad, in that the claims do not specify which arrestin detectable molecule would work with a given GPCR in detecting the GPCR activation pathway.

It is unpredictable to take any arrestin detectable molecule to use in detecting a GPCR activation pathway because all the three arrestins are different and their interaction with a GPCR differs on a number of factors.

Due to the large quantity of experimentation necessary to determine an arrestin detectable molecule such that it can be used in detecting a GPCR activation pathway, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that an arrestin can not be predicted based on a GPCR, and the breadth of the claims which fail to recite the arrestin and GPCR activation pathway, the specification fails to teach the skilled artisan how to make and use the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

Gyan Chandra
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08September 2004